

AMENDMENT

In the Claims:

The present amendment adds claims 51-57. According to 37 C.F.R. § 1.121(c), after entry of the present amendment, the following claims are in the case:

1. (Previously Amended) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent; and:

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- (a) a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; or
 - (b) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.

2. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises a targeting agent that binds to phosphatidylethanolamine.

3. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises a targeting agent that binds to phosphatidylserine.

4. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first anti-aminophospholipid antibody or antigen-binding fragment thereof.

5. (Original) The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first IgG or IgM anti-aminophospholipid antibody.

6. (Original) The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first scFv, Fv, Fab', Fab or F(ab')₂ antigen-binding fragment of an anti-aminophospholipid antibody.

7. (Original) The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first recombinant anti-aminophospholipid antibody, or antigen-binding fragment thereof.

8. (Original) The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first human, humanized or part-human chimeric anti-aminophospholipid antibody, or antigen-binding fragment thereof.

9. (Original) The kit of claim 4, wherein said targeting agent-therapeutic agent construct comprises at least a first monoclonal anti-aminophospholipid antibody, or antigen-binding fragment thereof.

10. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first aminophospholipid binding protein or an aminophospholipid-binding fragment thereof.

11. (Original) The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first phosphatidylserine binding protein or a phosphatidylserine-binding fragment thereof.

12. (Original) The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first phosphatidylethanolamine binding protein or a phosphatidylethanolamine-binding fragment thereof.

13. (Original) The kit of claim 10, wherein said targeting agent-therapeutic agent construct comprises at least a first Annexin V or kininogen or an aminophospholipid-binding fragment thereof.

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Cont 14. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first anticellular or cytotoxic agent.


15. (Original) The kit of claim 14, wherein said targeting agent-therapeutic agent construct comprises at least a first gelonin, ricin A chain or deglycosylated ricin A chain.

16. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises at least a first coagulant.

17. (Original) The kit of claim 16, wherein said targeting agent-therapeutic agent construct comprises at least a first Tissue Factor, dimeric Tissue Factor, trimeric Tissue Factor, polymeric Tissue Factor, mutant Tissue Factor, truncated Tissue Factor or a Tissue Factor derivative.

18. (Original) The kit of claim 1, wherein said targeting agent-therapeutic agent construct comprises an anti-phosphatidylserine antibody, or antigen binding fragment thereof, that is directly or indirectly attached to truncated Tissue Factor.

19. (Original) The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable formulation suitable for intravenous administration.


 20. (Original) The kit of claim 1, wherein said kit comprises, in distinct pharmaceutical compositions, said at least a first targeting agent-therapeutic agent construct in combination with said targeting agent-detectable agent construct.

21. (Original) The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the X-ray detectable compound bismuth (III), gold (III), lanthanum (III) or lead (II).

22. (Original) The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the detectable radioactive ion copper⁶⁷, gallium⁶⁷, gallium⁶⁸, indium¹¹¹, indium¹¹³, iodine¹²³, iodine¹²⁵, iodine¹³¹, mercury¹⁹⁷, mercury²⁰³, rhenium¹⁸⁶, rhenium¹⁸⁸, rubidium⁹⁷, rubidium¹⁰³, technetium^{99m} or yttrium⁹⁰.

23. (Original) The kit of claim 20, wherein said targeting agent-detectable agent construct comprises the detectable nuclear magnetic spin-resonance isotope cobalt (II), copper (II), chromium (III), dysprosium (III), erbium (III), gadolinium (III), holmium (III), iron (II), iron (III), manganese (II), neodymium (III), nickel (II), samarium (III), terbium (III), vanadium (II) or ytterbium (III).

24. (Original) The kit of claim 1, wherein said kit comprises said at least a first targeting agent-therapeutic agent construct in combination with said at least a second anti-cancer agent.



25. (Original) The kit of claim 24, wherein said at least a first targeting agent-therapeutic agent construct and said at least a second anti-cancer agent are comprised within a single pharmaceutical composition.

26. (Original) The kit of claim 24, wherein said at least a first targeting agent-therapeutic agent construct and said at least a second anti-cancer agent are comprised within distinct pharmaceutical compositions.

27. (Original) The kit of claim 24, wherein said at least a second anti-cancer agent is a chemotherapeutic agent, radiotherapeutic agent, anti-angiogenic agent or apoptosis-inducing agent.


28. (Original) The kit of claim 24, wherein said at least a second anti-cancer agent is an antibody-therapeutic agent construct comprising a second targeting antibody, or antigen-binding fragment thereof, that binds to a surface-expressed, surface-accessible or surface-localized component of a tumor cell, tumor stroma or tumor vasculature; wherein said targeting antibody or fragment thereof is operatively linked to a therapeutic agent.

29. (Original) The kit of claim 28, wherein said second targeting antibody, or antigen-binding fragment thereof, binds to a surface-expressed, surface-accessible, surface-localized, cytokine-inducible or coagulant-inducible component of intratumoral blood vessels of a vascularized tumor.

30. (Original) The kit of claim 29, wherein said second targeting antibody, or antigen-binding fragment thereof, binds to a component of intratumoral vasculature selected from the group consisting of an aminophospholipid, endoglin, a TGF β receptor, E-selectin, P-selectin, VCAM-1, ICAM-1, PSMA, a VEGF/VPF receptor, an FGF receptor, a TIE, $\alpha_v\beta_3$ integrin, pleiotropin, endosialin, an MHC Class II protein, VEGF/VPF, FGF, TGF β , a ligand that binds to a TIE, a tumor-associated fibronectin isoform, scatter factor/hepatocyte growth factor (HGF), platelet factor 4 (PF4), PDGF and TIMP.

31. (Original) The kit of claim 28, wherein said second targeting antibody, or antigen-binding fragment thereof, is operatively linked to gelonin, deglycosylated ricin A chain, Tissue Factor, truncated Tissue Factor or to an antibody, or antigen-binding fragment thereof, that binds to Tissue Factor or truncated Tissue Factor.

32. (Previously Amended) The kit of claim 1, wherein said kit comprises biologically effective amounts of:

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- (a) said at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;
 - (b) said targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and
 - (c) said at least a second anti-cancer agent.

Claims 33-42 previously cancelled

43. (Previously Amended) In combination, biologically effective amounts of:

- (a) a first composition comprising at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent;
- (b) a second composition comprising a targeting agent-detectable agent construct that comprises a second targeting agent that binds to an aminophospholipid operatively attached to a detectable agent; and
- (c) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.

44. (Previously Added) The kit of claim 20, wherein the targeting agent of said at least a first targeting agent-therapeutic agent construct and the targeting agent of said targeting agent-detectable agent construct are anti-aminophospholipid antibodies, or antigen-binding fragments thereof, obtained from the same antibody preparation or antibody-producing hybridoma.

45. (Previously Added) The combination of claim 43, wherein said first composition is a pharmaceutical composition.

46. (Previously Added) The combination of claim 43, wherein said second composition is a pharmaceutical composition.

E1 47. (Previously Added) The combination of claim 43, wherein said at least a second anti-cancer agent is admixed with said at least a first targeting agent-therapeutic agent construct to form a therapeutic cocktail.

48. (Previously Added) The combination of claim 43, wherein said at least a second anti-cancer agent is comprised within a composition distinct from said at least a first targeting agent-therapeutic agent construct.

49. (Previously Added) A kit comprising, in a pharmaceutically acceptable form, biologically effective amounts of at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent operatively attached to at least a first therapeutic agent, wherein said at least a first targeting agent binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor; and

- (a) a targeting agent-detectable agent construct that comprises a second targeting agent operatively attached to a detectable agent, wherein said second targeting agent binds to an aminophospholipid expressed on the luminal surface of blood vessels of a vascularized tumor; or
- (b) an anti-cancer agent.

50. (Previously Added) The kit of claim 1, wherein said kit comprises at least a first pharmaceutically acceptable liposomal formulation.

61 51. (New) A kit comprising, in a pharmaceutically acceptable form, therapeutically effective amounts of:

- (a) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent that binds to an aminophospholipid operatively attached to at least a first therapeutic agent; and
- (b) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.


52. (New) A kit comprising, in a pharmaceutically acceptable form, therapeutically effective amounts of:

- (a) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent operatively attached to at least a first therapeutic agent,

wherein said at least a first targeting agent binds to phosphatidylethanolamine expressed on the luminal surface of blood vessels of a vascularized tumor; and

- (b) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct.

53. (New) A kit comprising, in a pharmaceutically acceptable form, therapeutically effective amounts of:

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- (a) at least a first anti-cancer agent, wherein said at least a first anti-cancer agent is at least a first targeting agent-therapeutic agent construct that comprises at least a first targeting agent operatively attached to at least a first therapeutic agent, wherein said at least a first targeting agent binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor; and
 - (b) at least a second anti-cancer agent other than said at least a first targeting agent-therapeutic agent construct; wherein said at least a second anti-cancer agent:
 - (i) increases aminophospholipid expression in the endothelium of said blood vessels of said vascularized tumor or injures or induces apoptosis in the endothelium of said blood vessels of said vascularized tumor; or
 - (ii) kills tumor cells of said tumor or is an anti-angiogenic agent that inhibits metastasis of tumor cells.

54. (New) The kit of claim 53, wherein said at least a second anti-cancer agent increases aminophospholipid expression in the endothelium of said blood vessels of said vascularized tumor or injures or induces apoptosis in the endothelium of said blood vessels of said vascularized tumor.

55. (New) The method of claim 54, wherein said at least a second anti-cancer agent is taxol, vincristine, vinblastine, neomycin, a combretastatin, a podophyllotoxin, TNF- α , angiostatin, endostatin, vasculostatin, an $\alpha_v\beta_3$ antagonist, a calcium-flux inducing agent, a calcium ionophore, H₂O₂, thrombin, an inflammatory cytokine or interleukin-4.

56. (New) The kit of claim 53, wherein said at least a second anti-cancer agent kills tumor cells of said tumor or is an anti-angiogenic agent that inhibits metastasis of tumor cells.

57. (New) The kit of claim 56, wherein said at least a second anti-cancer agent is an anti-tumor cell immunoconjugate, a chemotherapeutic agent or an anti-angiogenic agent.
